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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SHIBUYA, MARK LANCE	
ART UNIT	**PAPER NUMBER**
1639	

DATE MAILED: 10/29/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/070,128	BRIAND, JACQUES	
	Examiner	Art Unit	
	Mark L. Shibuya	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 August 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) *12-16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-11 and 17-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/27/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-19 are pending. Claims 12-16 are withdrawn from consideration as being drawn to a non-elected invention. Claims 1-11 and 17-19 are examined.

Election/Restrictions

2. Applicant's election of Group I, claims 1-11 and 17-19 in the reply filed on 8/19/04 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). As a species, applicant elected a chemical shift in said first dimension that is a IH, 3H, 1 IB, 13C, 15N, 19F, 295, or 31 chemical shift.

Priority

3. This application is the national stage entry of PCT/US00/26949, and claims benefit of Provisional application 60/156,557, filed 8/29/1999.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-11 and 17-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 19 recite the language "incubation times", which renders the claims vague and indefinite, because the term "incubation times " is a relative term that renders the claim indefinite. The term "incubation times" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of skill in the art would not be reasonably apprised of the metes and bounds of the invention.

Claim 2 recites the term "biomolecule", which renders the claim indefinite, because it is unclear what molecular structures are or are not encompassed by the term. The term "biomolecule" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of skill in the art would not be reasonably apprised of the metes and bounds of the invention.

Claim 4 misspells the word "dimensional" in line 3. Claim 11, appears to recite an improper Markush limitation by omitting the connector "and" in line 2.

Claim 18 recites the language "at a selected time", which renders the claim vague and indefinite, because it seems to read on a mental step and it is unclear as to who selects the time or what time is selected.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

5. Claims 1-4, 6, 7, 9-11, 17, 18, and 19 are rejected under 35 U.S.C. 102(e) as being anticipated by Moore et al., (US 2003/0143757).

The claims are drawn to methods of identifying compounds that interact with a target molecule comprising the steps of: a) mixing a substrate, product or ligand of a target with at least one chemical compounds b) generating a first spectrum that displays either a chemical shift in the first dimension or a chemical shifts in the other dimension of substrate, product or ligand in step a); c) exposing substrate, product or ligand and mixture of chemical compounds in step a) to a target molecule for one or more incubation times; d) generating a second spectrum that displays either a chemical shifts in the first dimension or a chemical shifts in the other dimension of substrate or product in step a) that has been exposed to the target molecule in step c) in the presence of one

or mixture of chemical compounds in step a); e) comparing said first spectrum and second spectrum after one or more said incubation times in step c) to determine at least one difference between said first spectrum and second spectrum, the differences observed along either or both chemical shift dimensions identifying the transformation of said substrate and classifying the presence of one or more compounds that are substrates, products or ligands that interact with said target molecule; and variations thereof.

Moore et al., (US 2003/0143757), at para [0052]-[0059], [0075]-[0082], [0139] teaches obtaining an NMR spectrum of a ligand, exposing the ligand to the target and generating a subsequent NMR spectrum of the ligand. Moore et al. state:

According to one preferred embodiment, the determination of binding is achieved by the NMR method of line broadening, relaxation filtering or a combination of the two and comprises the steps of: i) obtaining a one-dimensional NMR spectrum of said drug core in the absence of said target; ii) mixing the target with the drug core at a molar ratio of between 1:1 and 1:100. iii) subjecting said mixture to nuclear magnetic resonance for a period of time sufficient to obtain a one-dimensional spectrum; and iv) comparing the spectra obtained in steps i) and iii) to determine if said drug core has bound to said target.

Moore et al., (US 2003/0143757), at para [0052]-[0056]. Moore contemplates testing multiple drug cores in the same sample, which reads on mixing a substrate, product or ligand with at least one compound, and wherein the mixture comprises between 2 and 100 chemical compounds (claim 6). Moore contemplates targets that are protein, enzymes, peptides, nucleic acids, etc., which are biomolecules (claim 2). Moore teaches individual compartmentalization of compounds wherein the compounds are provided in multi-well plates, or attached to solid media or beads.

6. Claims 1-11, 18, and 19 are rejected under 35 U.S.C. 102(b) as being anticipated by Thompson et al., Proc. Natl. Acad. USA, Vol. 94, pp. 14249-14254 (Dec. 1997).

Thompson et al. at the abstract, p. 14249, para 5-p. 14250, para 3, Fig. 1, p. 14252, para 3, Fig. 4, teach the proton NMR characterization of inhibitors of the cysteine protease, a biomolecule, wherein the inhibitors were synthesized with the isotope 3H; followed by NMR analysis of cathepsin K adducts with inhibitors, wherein the protease and inhibitors are incubated with 2-(*N*-morpholino)ethane-sulfonic acid (Mes)/NaCl/Cys for fixed times depending upon inhibitor concentration, whereupon the reactions are quenched by dialysation into 90% water/10% D_2O, 50 mM acetate-d_3, 250 mM NaCl, and 2mM L-Cys.

7. Claims 1-11, 18, and 19 are rejected under 35 U.S.C. 102(b) as being anticipated by Hajduk et al., J. Am. Chem. Soc. 1997, vol. 119, pp. 12257-12261 (IDS filed 2/27/02).

Hajduk et al., throughout the publication, and at the abstract, p. 12257, para 2-p. 12258, Table 1, Figures 2-4, teach identifying compounds that bind to macromolecules by one-dimensional NMR, which exploits changes in either the relaxation rates or diffusion rates of a small compound, that occurs upon binding to the biomolecules. Hajduk et al., teaches a mixture of 2-phenylimidazole, which binds to the FK506 binding protein (FKBP) and eight compounds that do not bind to the protein; Figures 2-4 depict NMR plots of 1H NMR spectra for 2-phenylimidazole alone and binding to FKBP; and

spectra for the ligand 5-cyano-4'hydroxybiphenyl, which binds to the matrix metalloproteinase stromelysin, and of said 5-cyano-4'hydroxybiphenyl binding to the catalytic domain of the proteolytic enzyme stromelysin. Hajduk et al. also teach 5-cyano-4'hydroxybiphenyl in combination with eight other compounds that do not bind stromelysin.

8. Claims 1-4, 6, 7, 9-11, 17 and 19 are rejected under 35 U.S.C. 102(b) as being anticipated by Fesik et al., (WO 98/48264).

Fesik et al., (WO 98/48264), throughout the publication, and at p. 1, lines 2-4, p. 2, line 23-p. 3, line 12, p. 4, line 18-p.4, line 33, p. 7, line 32-p. 8, line 37, p. 10, lines 10-19, p. 10, line 35-p. 11, line 2, teaches: a) generating a first T2- or diffusion-filtered proton spectrum of one or a mixture of chemical compounds; b) exposing one or a mixture of chemical compounds to the target molecule; c) generating a second T2- or diffusion filtered proton spectrum of one or a mixture of chemical compounds that has been exposed to the target molecule in step (b); and d) comparing said first and second T2- or diffusion-filtered proton spectra to determine differences between said first and said second spectra, the differences identifying the presence of one or more compounds that are ligands which have bound to the target molecule. Additional steps comprise the steps of e) generating a T2- or diffusion-filtered proton spectrum of each compound in the mixture f) exposing each compound in the mixture individually to the target molecule, g) generating a T2- or diffusion-filtered proton spectrum of each compound in the mixture after exposure to the target molecule h) comparing each

spectrum generated in step g) to the first spectrum generated from the target molecule alone to determine differences in any of those compared spectra, the differences identifying the presence of a compound that is a ligand which has bound to the target molecule; wherein the target is a polypeptide, which is a biomolecule. Fesik et al. teaches use of a sample changer with a total of 60 samples that can be run unattended and computer programs to facilitate transfer and automatic processing of multiple one-dimensional NMR data.

9. Claims 1-4, 6, 7, 9-11, 17 and 19 are rejected under 35 U.S.C. 102(b) as being anticipated by Fesik et al., (WO 97/18469).

Fesik et al., (WO 97/18469), throughout the publication, and at p. 1, lines 2-4, p. 3, lines 7-28, p. 7, line 32-p. 8, line 2, p. 8, line 37-p. 9, line 28, p. 11, lines 32-36, p. 14, lines 10-17, p. 18, line 25-p. 31, line 9; teaches screening chemical compounds for binding to a given target biomolecule by a process involving the steps of a) first generating a first two-dimensional 15N/1H NMR correlation spectrum of a 15N-labeled target molecule; b) exposing the labeled target molecule to one or a mixture of chemical compounds; c) next, generating a second two-dimensional 15N/1H NMR correlation spectrum of the labeled target molecule that has been exposed to one or a mixture of compounds in step (b); and d) comparing said first and second two dimensional15N/1 H NMR correlation spectra to determine differences between said first and said second spectra, the differences identifying the presence of one or more compounds that are ligands which have bound to the target molecule. Fesik et al. teaches use of a sample

changer with a total of 60 samples that can be run unattended and computer programs to facilitate transfer and automatic processing of multiple one-dimensional NMR data. Fesik et al. teach that individual compounds, which may be interpreted as targets, that can be selected inter alia on the basis of size (molecular weight = 100-300) and molecular diversity. Compounds in the collection can have different shapes (e.g., flat aromatic rings(s), puckered aliphatic rings(s), straight and branched chain aliphatics with single, double, or triple bonds) and diverse functional groups (e.g., carboxylic acids, esters, ethers, amines, aldehydes, ketones, and various heterocyclic rings) for maximizing the possibility of discovering compounds that interact with widely diverse binding sites.

10. Claims 1, 2, 3, 10, 11, and 19 are rejected under 35 U.S.C. 102(b) as being anticipated by Deem et al., (WO 96/30849).

Deem et al., throughout the publication and at p. 10, line 1-p. 11, line 8, p. 12, lines 26-36, p. 15, line 14-p. 17 line 14, p. 22, line 4-p. 23, line 6, p. 25, lines 18-27, p. 41, lines 21-24, p. 50, lines 18-36, teach NMR measurements of molecules ("binders") that bind to targets, wherein the targets include proteins, (including enzymes), and wherein comparing spectra comprises an algorithm or a computer algorithm.

11. Claim 19 is rejected under 35 U.S.C. 102(b) as being anticipated by Withers et al., (US 5,716,812).

Claim 19 is drawn to a method of identifying compounds that interact with a target molecule comprising the steps of: a) exposing substrate to a target molecule for one or more incubation times; b) generating one or more spectra at one or more incubation times of said substrate and said target molecule of step a); c) exposing said substrate and one or mixture of chemical compounds for one or more incubation times; d) generating one or more spectra at one or more incubation times of said substrate, said target molecule and said compounds of step c); e) comparing at least one spectrum of step b) with at least one spectrum of step d) to determine at least one difference between said spectrum of step b) with said spectrum of step d) the differences observed along either or both chemical shift dimensions identifying the transformation of said substrate and classifying the presence of one or more compounds that are substrates, products or ligands that interact with said target molecule.

Withers et al., throughout the patent and at col. 4, lines 35-40, teach NMR analysis of a substrate in the active site of an enzyme and at, e.g., Example 5, col. 13, lines 54-67, teach 1H-NMR analysis of products of enzymatic transglycosylation reactions.

Conclusion

12. Claims 1-11 and 17-19 are rejected.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark L. Shibuya whose telephone number is (571) 272-0806. The examiner can normally be reached on M-F, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Mark L. Shibuya
Examiner
Art Unit 1639

PADMASHRI PONNALURI
PRIMARY EXAMINER

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